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| 09/827,846 | 04/06/2001 | Shinichi Eda | RDC 12320 Div. | 7993 |

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| EXAMINER | |
|---|---|
| GABEL, GAILENE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | |

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/827,846 | Applicant(s) EDA ET AL. | |
|---|---|---|---|
| | Examiner Gailene R. Gabel | Art Unit 1641 | |

*-- The MAILING DATE of this c mmunication appears on the cover she t with the corresp ndence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Amendment Entry*

1. Applicant's amendment and response filed 3/14/02 in Paper No. 4 is acknowledged and has been entered. Claim 18 has been cancelled. Claim 21 has been amended. Accordingly, claims 1-17 and 19-21 are pending and are under examination.

### ***Rejections Withdrawn***

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. In light of Applicant's argument, the rejection of claim 21 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. The rejection of claim 18 under 35 U.S.C. 103 (a) is withdrawn in light of Applicant's cancellation of the claim.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-8, 10-12, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grange et al. (Journal of Immunological Methods,1977) in view of Lindmo et al. (Journal of Immunological Methods, 1990) for reason of record.

Grange et al. teach a reagent comprising light scattering microparticles having specific binding partners (antigens and antibodies) covalently bound thereto for use in agglutination or nephelometric assays (see Abstract). Grange et al. teach that sensitivity in nephelometric assays is dependent upon the reactivity (affinity) of the immunological binding partners being titered, the ratio of antigen to antibody- near equivalence, and the medium in which reaction takes place (see Introduction). Grange et al. specifically teach that light scatter is amplified by increasing "molecular size" antigens or antibodies by adsorbing them into the microparticles with light scattering properties. Grange et al. also teach that intensity of light scatter by a given suspension of microparticles is dependent on the size and number of the particles. Other factors that influence the intensity of light scatter includes shape, dimension, refractive index, and polydispersity of the microparticles (see page 366, last paragraph bridging to page 367). Grange et al. further teach the influence of wavelength, microparticle

concentration, angle of observation, and reaction time in agglutinated (aggregated) particles (see Figures 1-8). In determining reactivity (specificity) between binding partners coated into microparticles, the light scattered by microparticles which have interacted show significantly increased light scatter and is proportionate to the concentration of the antigen (see page 373).

Grange et al. differ in failing to teach differential characterization between two microparticle populations. Grange et al. also fails to teach differential reactivity and dissociation constants between two immunological binding partners coated therein.

Lindmo et al. teach reagents having two distinguishable microparticle types for use in immunometric assays. Lindmo et al. specifically teach the two populations of microparticles as distinctly having 7um and 10um in diameter. Both microparticle types are coated with binding partners (antibody) having the same specificity but different reactivity (affinity) and having association constants of $3.2 \times 10^{10}$ and $3.2 \times 10^{9}$ for the 7um and 10um, respectively (see Introduction). Lindmo et al. teach that at low antigen concentrations, binding preferentially occurs on the high reactivity microparticles and the low reactivity microparticles show increase in binding with increasing antigen concentration even after binding to the high affinity particles has been saturated. This results in increase in dynamic range for the assay without compromising the high sensitivity provided by the high affinity particle (see page 184, column 2, last paragraph). Figure 2A shows a double standard curve obtained by differentially plotting the mean channel number of the fluorescence distribution for both microparticle populations as a function of antigen concentration in the sample (see page 186, second, third and fourth paragraphs). High reactivity microparticles exhibit significant binding in comparison to low reactivity microparticles at 0.2 ug/l concentration (see Figure 2A and page 186). Lindmo et al. teach that in binary mixtures, the measurements obtained

from high reactivity microparticles provide high precision in the low concentration range whereas measurements from low reactivity microparticles provide precision in the high concentration range (see page 187, second column). Lindmo et al. also teach populations of microparticles with uniform sizes at a given ratio or concentration separated by differing sizes and immunological binding partners with specific reactivities, i.e. dissociation constants, or association constants at a given ratio and concentration (see Lindmo et al., page 184-185).

One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teachings of Lindmo of a reagent comprising a binary mixture of microparticles into the microparticulate reagent mixture of Grange because Lindmo specifically taught that his binary microparticles with high and low reactivities can easily be incorporated with the concept of various mixtures of distinguishable microparticles coated with antibodies of different specificities in a simultaneous or homogeneous assay of analytes such as in the teaching of Grange.

5. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Grange et al. (Journal of Immunological Methods,1977) in view of Lindmo et al. (Journal of Immunological Methods, 1990) and in further view of Sutton et al. (US 5,330,891) for reason of record.

Grange et al. and Lindmo et al. have been discussed supra. Grange et al. and Lindmo et al. differ in failing to teach that the analyte tested for is nucleic acid and the binding partners are oligonucleotide probes.

Sutton et al. disclose microparticulate reagent for use in detecting nucleic acids wherein the microparticulates have polyoxyalkylene side chains having an oligonucleotide probe covalently attached thereto through reactive groups. The oligonucleotide probe is complementary to the nucleic acid analyte.

One of ordinary skill in the art at the time of the instant invention would have reasonable expectation of success in covalently attaching oligonucleotide probes such as taught by Sutton into the microparticles taught by Grange and Lindmo in order to create a reagent for detecting nucleic acid analytes because oligonucleotide probes constitute obvious variations of species of binding partners which are specific for nucleic acids and which are routinely varied in the art and which have not been described as being critical to the practice of the invention.

6. Claims 13-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grange et al. (Journal of Immunological Methods,1977) in view of Lindmo et al. (Journal of Immunological Methods, 1990) and in further view of Harchali et al. (Clin. Chem.,1994).

Grange et al. and Lindmo et al. have been discussed supra. Grange et al. and Lindmo et al. differ in failing to teach the composition of the microparticles in the reagent wherein the microparticles are coated with binding partners (antigens) with varying defined epitopic specificities.

Harchali et al. teach light scattering microparticles which are polyacrylic, polyfunctional, copolymerized microparticles conjugated with antigens of defined

epitopic specificity used for agglutination assays and microparticle-enhanced nephelometric assays (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the use of two types of particles conjugated with antigens of differing reactivity as taught by Lindmo and further apply the teachings of Harchali in incorporating defined epitopic specificities, with the teachings of Grange in manufacturing microparticles for use in agglutination assays because Lindmo specifically taught binary microparticle reagents with high and low reactivities can be combined with the concept of using a mixture of distinguishable particles coated with antibodies of different specificities or same specificity but different reactivity towards differing epitopes in a simultaneous or homogeneous assay of antigens such as in the teachings of both Grange and Harchali.

***Response to Arguments***

7. Applicant's arguments filed 3/14/02 have been fully considered but they are not persuasive.

A) Applicant argues that the teachings of Grange with Lindmo are not combinable because the microparticles taught by Grange and Lindmo are based on totally distinct assay principles, namely, microparticle light scattering agglutination assay and flow cytometric assay, respectively. Applicant argues that in assays for flow cytometry, there is no aggregation of microparticles, rather they are determined for each

particle individually. Applicant, therefore, contends that one of ordinary skill would not be motivated to create any reagent based on this combination.

In response, while there would have been no motivation to combine the microparticles taught by Grange with that of Lindmo for ***use*** as reagent in a method of microparticle enhanced agglutination assay, the teaching of structural requirements of the microparticles taught by Grange is in itself combinable with the teaching of structural requirements of microparticles taught by Lindmo. Specifically, Grange teaches a reagent comprising light scattering microparticles having specific binding partners covalently bound thereto. Grange teaches that different immunological reactivities of the immunological binding partners immobilized into the particles can be tittered. Lindmo teaches reagents having two distinguishable microparticle types having distinct sizes, i.e. 7um and 10um in diameter. Both microparticle types are coated with immunological binding partners having the same specificity but different reactivity and having association constants of $3.2 \times 10^{10}$ and $3.2 \times 10^{9}$ for the 7um and 10um, respectively. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teachings of Lindmo of a reagent comprising a binary mixture of microparticles into the microparticulate reagent mixture of Grange because Lindmo specifically taught that his binary microparticles with high and low reactivities can easily be incorporated with the concept of various mixtures of distinguishable microparticles coated with antibodies of different specificities in a simultaneous or homogeneous assay of analytes such as in the teaching of Grange.

Further, it has been held that a recitation with respect to the manner in which a claimed product is intended to be employed does not differentiate the claimed product from a prior art product satisfying the claimed structural requirements. *Ex parte Masham 2 USPQ2d 1647 (1987).* Specifically, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

In response to applicant's arguments, the recitation "for (use) in an agglutination assay" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

B) Applicant argues that the teachings of Grange and Lindmo are not combinable with that of Harchali because the microparticles taught by Grange, Lindmo, and Harchali are based on totally distinct assay principles, namely, microparticle light

scattering agglutination assay, flow cytometric assay, agglutination assay, respectively. Applicant argues that assays for flow cytometry are distinct from agglutination assays as there is no aggregation of microparticles, rather they are determined for each particle individually. Applicant, therefore, contends that one of ordinary skill would not be motivated to create any reagent based on this combination.

In response, while there would have been no motivation to combine the microparticles taught by Grange with that of Lindmo and further with that of Harchali for ***use*** as reagent in a method of microparticle enhanced agglutination assay, the teaching of structural requirements of the microparticles taught by Grange and Lindmo are themselves combinable with the teaching of structural requirements of microparticles taught by Harchali. Specifically, Grange teaches a reagent comprising light scattering microparticles having specific binding partners covalently bound thereto. Grange teaches that different immunological reactivities of the immunological binding partners immobilized into the particles can be tittered. Lindmo teaches reagents having two distinguishable microparticle types having distinct sizes, i.e. 7um and 10um in diameter. Both microparticle types are coated with immunological binding partners having the same specificity but different reactivity and having association constants of $3.2 \times 10^{10}$ and $3.2 \times 10^{9}$ for the 7um and 10um, respectively. Harchali was incorporated thereto for teaching light scattering microparticles which are polyacrylic, polyfunctional, copolymerized microparticles conjugated with antigens of defined epitopic specificity. It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the use of two types of particles conjugated with antigens of differing reactivity

as taught by Grange and modified by Lindmo with the teachings of Harchali in incorporating defined epitopic specificities, because Lindmo specifically taught that binary microparticle reagents with high and low reactivities can be combined with the concept of using a mixture of distinguishable particles coated with antibodies of different specificities or same specificity but different reactivity towards differing epitopes in a simultaneous or homogeneous assay of antigens such as in the teachings of both Grange and Harchali.

Further, it has been held that a recitation with respect to the manner in which a claimed product is intended to be employed does not differentiate the claimed product from a prior art product satisfying the claimed structural requirements. *Ex parte Masham 2 USPQ2d 1647 (1987).* Specifically, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

In response to applicant's arguments, the recitation "for (use) in an agglutination assay" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the

process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

8. For reasons aforementioned, no claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday 6:00 AM to 3:30 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
June 1, 2002

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
06/03/02